Kinetics of acetaminophen absorption and gastric emptying in man

Eight healthy male volunteers ingested an aqueous solution containing acetaminophen (20 mg/kg) and a nonabsorbable isotopic marker. The concentrations of unconjugated acetaminophen in samples of blood plasma taken at frequent intervals were measured by gas-liquid chromatography. The data points followed a smooth curve in most cases and were fitted to the classical two-compartment pharmacokinetic model to obtain K_A, the apparent first-order rate constant for absorption from the gastrointestinal tract. Gastric emptying was measured simultaneously from serial scintiscans of the subject's abdomen. The subjects were also studied after intramuscular injection of meperidine (150 mg) and pentazocine (60 mg) with and without naloxone (1.2 mg). The acetaminophen absorption curves and gastric emptying patterns were consistent with negligible absorption from the stomach. A new model is proposed in which the conventional single compartment used to represent the gastrointestinal tract is replaced by two compartments: one represents the stomach and the other the small intestine, from which absorption occurs rapidly. Pharmacokinetic analysis using this model showed good agreement in all cases, and provided an estimate of K_A, the first-order rate constant for drug transfer from the intestinal lumen into the systemic circulation. The mean half-time for transfer was 6.8 ± 0.9 min. As expected, K_A* was greater than K_G (the first-order rate constant for gastric emptying), showing that gastric emptying was rate-limiting in the absorption of acetaminophen. The value of K_A* was greater than K_A and the two were not related. The value of K_A was not equal to K_G in most studies because gastric emptying was not a single exponential process.*

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Most drugs are believed to be absorbed from the alimentary tract by passive diffusion, and on theoretical grounds absorption from a solution should occur in accordance with a first-order process. When a drug is administered as a solid dosage-form deaggregation and particle dissolution precede absorption,[16] and absorption may not be a monoexponential process. If a drug is administered in aqueous solution (assuming that pH changes do not cause precipitation), it should be immediately available for absorption, but absorption of most drugs from the stomach is much slower than from the small intestine.[5, 7, 9, 13] Consequently, the rate at which a drug is transferred from the stomach to the duodenum is an important determinant of the

Received for publication Feb. 27, 1978.
Accepted for publication June 3, 1978.
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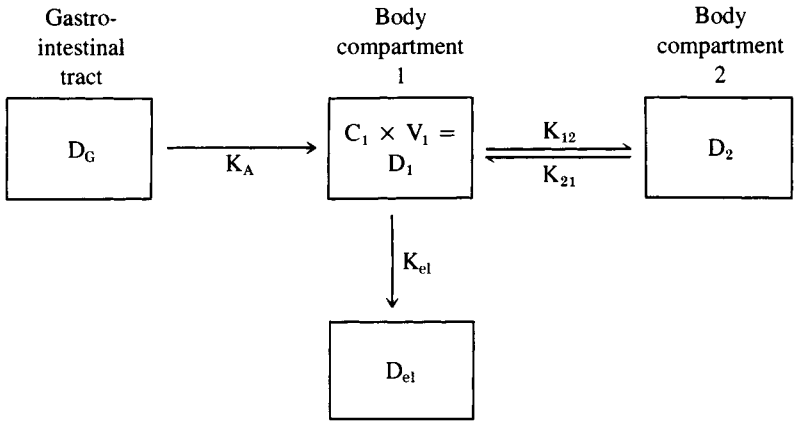


Schema 1. Two-compartment open model for oral administration.

overall absorption rate. We have previously shown that the area under the plasma concentration–time curve is proportional to the percentage of an orally administered solution of acetaminophen emptied from the stomach of normal subjects during the first hour.[9]

In pharmacokinetic analysis of plasma drug concentration–time data, a first-order rate constant (K_A) is often calculated for absorption from the gastrointestinal tract.[3] This constant is necessarily a hybrid, dependent upon the rates of all contributing processes but governed primarily by the slowest or rate-limiting step.

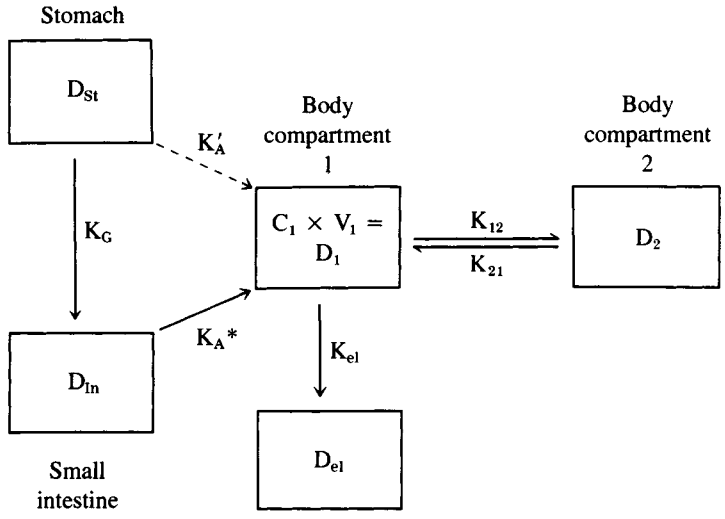
The hypothesis that gastric emptying rather than transmucosal transfer from the lumen of the small intestine is rate-limiting for rapidly absorbed drugs has apparently not been tested by the appropriate pharmacokinetic analysis. In this paper we describe a new pharmacokinetic model with four compartments, namely, two body compartments and one each for the stomach and the site of most rapid absorption in the small intestine. The model was tested by studying the absorption of orally administered acetaminophen in aqueous solution, with simultaneous radioisotopic measurement of gastric emptying in healthy volunteers, and was found to be entirely consistent with the experimental data.

Methods

Gastric emptying. Gastric emptying and acetaminophen absorption were measured simultaneously in eight adult male volunteers aged 26 to 39. After fasting overnight, within 2 min each subject drank orange juice (400 ml) containing acetaminophen (20 mg/kg) in solution together with ^{113m}In DTPA* (300 μCi) as a nonabsorbable isotopic marker for the emptying measurements. Gastric emptying rate was determined directly by serial scintiscans of the subject's abdomen and summing the counts over the stomach area.[4] The measurement of emptying between the time of ingestion of the drink and performance of the first scan was made by the method of Colmer, Owen, and Shields.[2] All results were corrected for isotopic decay, and the first-order rate constants for gastric emptying were determined by regression analysis.

Acetaminophen absorption. Serial blood samples were taken at frequent intervals for 8 hr after ingestion for assessment of absorption. The plasma was stored frozen and the concentration of unchanged acetaminophen was measured by gas-liquid chromatography.[12] No food, drink, or tobacco was permitted for 4 hr after acetaminophen, and the subjects remained supine throughout this period. Initially each subject was studied on two occasions at least 7 days apart. On one occasion an intramuscular injection of meperidine (150 mg) was given 30 min before the acetaminophen solution, and on the other occasion subjects received placebo injection of 0.9% saline. The order of narcotic

*Chelate of indium-113m with diethyltriaminepenta-acetic acid.



Schema 2. Proposed model with two body compartments and separate compartments representing the stomach and the small intestine.

and placebo administration was determined on a random basis. Four of the 8 subjects were studied on two further occasions: (1) 30 min after intramuscular pentazocine (60 mg) and (2) 30 min after intramuscular pentazocine (60 mg) and immediately after intravenous naloxone (1.2 mg).

Pharmacokinetic models. Two different compartmental models were used for the analysis of the plasma concentration of unconjugated acetaminophen at various times after ingestion.

Schema 1 shows a conventional compartmental model with one compartment representing the gastrointestinal tract and two compartments representing the body. The apparent absorption rate constant (K_A) is the assumed first-order rate constant for the transfer of drug from the gastrointestinal into the central body compartment (compartment 1), K_{12} and K_{21} are the rate constants for transfer into and out of the second body compartment (compartment 2), respectively, and K_{el} is the elimination rate constant from the central compartment. D_G, D_1, D_2, and D_{el} are the quantities in the gastrointestinal tract, compartment 1, compartment 2, and the quantity of eliminated drug, respectively.

Schema 2 shows a similar model but with the gastrointestinal tract represented by two compartments to correspond to the stomach and the small intestine. The constant K_G is the first-order rate constant for gastric emptying and K_A^* is the rate constant for transfer of drug from the small intestine into the systemic circulation. K_A' is the rate constant for absorption from the stomach. It was assumed to very small for acetaminophen and was neglected subsequently. D_{St}, D_{In}, D_1, D_2, and D_{el} are the quantities in the stomach, small intestine, body compartment 1, body compartment 2, and the quantity of eliminated drug, respectively.

Computer analysis. Analog computer programs were constructed for these two models and the line of best fit to the data points was drawn by eye using an X-Y recorder. In the model shown in Schema 2 the value of K_G found from measurements of gastric emptying was used as a constant in the computer program. The results of gastric emptying measurements showed that in many studies monoexponential emptying was preceded by a short period during which a proportion of the dose passed rapidly through the pylorus as a bolus or "squirt." The computer program was modified to accommodate this and other types of gastric emptying pattern observed in the study (see the section on results).

The equation for C_1, the concentration of drug in the central compartment for the model of Schema 1, was that given in standard texts.[16]

The equation for C_1 for the model in Schema 2 was found using Laplace transforms and the antitransform obtained by established methods.[1]

$$C_1 = \frac{F \cdot D_0 \cdot K_A^*}{V_1}\left[\frac{f_2K_G(K_{21} - K_G) \cdot e^{-K_G(t-t_{LAG})}}{(K_A^* - K_G)(\alpha - K_G)(\beta - K_G)} + \left\{\frac{f_2K_G + f_1(K_G - K_A^*)}{(K_G - K_A^*)(\alpha - K_A^*)(\beta - K_A^*)}\right\} \cdot (K_{21} - K_A^*) \cdot e^{-K_A^*(t-t_{LAG})} + \left\{\frac{f_2K_G + f_1(K_G - \alpha)}{(K_G - \alpha)(K_A^* - \alpha)(\beta - \alpha)}\right\} \cdot (K_{21} - \alpha) \cdot e^{-\alpha(t-t_{LAG})} + \left\{\frac{f_2K_G + f_1(K_G - \beta)}{(K_G - \beta)(K_A^* - \beta)(\alpha - \beta)}\right\} \cdot (K_{21} - \beta) \cdot e^{-\beta(t-t_{LAG})}\right] \quad (1)$$

where V_1– is the apparent volume of distribution for the central body compartment,

F– is the fraction of the administered dose (D_0) that ultimately reaches the systemic circulation,

f_1– is the fraction of this quantity of drug ($F.D_0$) that is emptied rapidly from the stomach in the first short interval of time as a bolus or "squirt,"

f_2– is the fraction that is emptied exponentially from the stomach with rate constant K_G (min^{-1}),

t– is elapsed time after ingestion,

t_{LAG}– is the interval between ingestion and the start of gastric emptying,

α and β– are, respectively, the fast and slow disposition rate constants for the two-compartmental body model, as defined by

$$\alpha + \beta = K_{12} + K_{21} + K_{el}$$
$$\alpha \cdot \beta = K_{21} \cdot K_{el}$$

and K_{12}, K_{21} and K_{el} are defined by Schema 2.

It is assumed that the fraction of the dose reaching the systemic circulation is the same for the initial bolus and the exponentially released portions. In the special case where f_1 is zero, Equation 1 reduces to the same equation as that for exponential drug release from a sustained-release preparation into the gastrointestinal tract.[17]

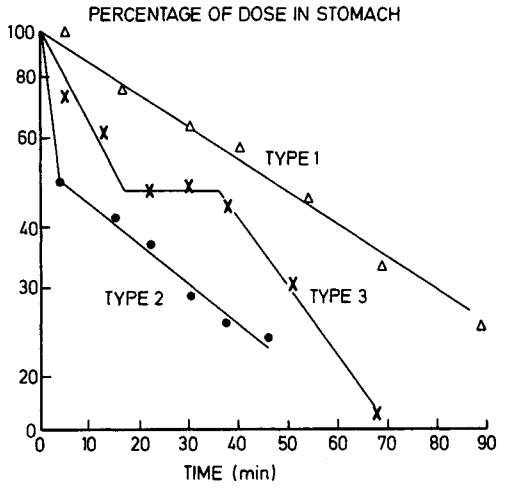


Fig. 1. Gastric emptying patterns in Subject 2, pentazocine-naloxone study (Type 1 gastric emptying), Subject 3, control study (Type 2 gastric emptying), and Subject 2, control study (Type 3 gastric emptying).

A nonlinear optimization method based on the simplex algorithm of Nelder and Mead[8] was used to refine the estimates found from the analog computer. The parameter estimates optimized on a digital computer were: FD_0/V_1; K_{12}; K_{21}; K_{el}; K_A (Schema 1) or K_A^* (Schema 2); t_{LAG}. For the model of Schema 2, values of K_G, f_1, and f_2 were constants derived from analysis of gastric emptying patterns. Individual data points were weighted by the method recommended by Ottaway.[11]

Multicompartmental analysis of plasma concentration–time data points following extravascular administration yields estimates of the rate constants for the (assumed) first-order processes of absorption, distribution, and elimination. The general form of the equation relating concentration (C_1) in compartment 1 to time after administration for the model of Schema 1 is:

$$C_1 = \sum_{i=1}^{3} A_i \cdot e^{-a_i \cdot (t - t_{LAG})}$$

Although the exponential terms a_1, a_2, and a_3 for a 2-compartment model may be assigned values equal to K_A, α, and β, they are not necessarily in this order.

Table I. *Rate constant for gastric emptying (K_G) and lag time in studies exhibiting a monoexponential emptying pattern (Type 1)*

Subject	*Treatment*	K_G *(min^{-1})*	*Lag time (min)*
1	Control	0.0420	5
2	Meperidine	0.0172	35
2	Pentazocine	0.0063	0
2	Pentazocine/naloxone	0.0146	0
3	Pentazocine	0.0132	0
7	Pentazocine/naloxone	0.0293	8

Table II. *Fraction (f_1) of dose emptied as an initial bolus and rate constant for subsequent gastric emptying (K_G); Type 2 emptying pattern*

Subject	*Treatment*	f_1 *(%)*	K_G *(min^{-1})*
1	Pentazocine/naloxone	60	0.0147
3	Control	46	0.0184
3	Pentazocine/naloxone	21	0.0123
4	Control	15	0.0268
5	Control	9	0.0386
6	Control	34	0.0503
7	Control	19	0.0533
8	Control	65	0.0174

For absorption of acetaminophen from an aqueous solution, the slow disposition rate constant (β) is smaller than the apparent absorption rate constant (K_A), and is by convention smaller than the fast disposition rate constant (α). The two remaining exponential terms cannot be assigned to α and K_A unless experimental data are available from studies using the intravenous route of administration or comparing several formulations given orally.[15] In the present study, however, the main effect of the narcotic analgesics was on gastric emptying (and thus K_A). The procedure adopted for each subject who received up to four treatments was allocation of the smallest exponential terms to β, and the near-constant terms to α: values of K_A were then found to alter with treatment in the expected way.

A similar dilemma arises in the identification of the exponential terms of the integrated equation for the model of Schema 2. The general form of Equation 1 is:

$$C_1 = \sum_{i=1}^{4} A_i \cdot e^{-a_i(t-t_{LAG})}$$

where the A_i terms are defined by the respective terms in Equation 1. In the nonlinear optimization, a_1 was a supplied constant equal to K_G and a_3 was identified as β. Values of a_2 or a_4 were assigned to α after comparing them with the estimates of α obtained from the analysis according to the model of Schema 1. The remaining exponential term was assigned to K_A*. In all cases good agreement was found between the pharmacokinetic values obtained by the analog and digital methods.

Results

Gastric emptying. Three different patterns of emptying were observed and were designated Type 1, 2, and 3 as follows:

Type 1. A monoexponential gastric emptying pattern commencing immediately after ingestion of the solution or preceded by an interval or lag period during which no emptying occurs.

Type 2. A biphasic gastric emptying pattern in which a fraction (f_1) of the total administered dose emptied rapidly from the stomach within the first 10 to 15 min, followed by a monoexponential decrease of the remaining fraction (f_2). The small number of points in the first short time interval did not allow a distinction to be drawn between a fast monoexponential emptying and an "instantaneous" squirt or bolus. Preliminary analysis showed that the calculated plasma concentration–time curves were virtually identical for both cases, and so the early emptying pattern was regarded as an initial bolus.

Type 3. A biphasic gastric emptying pattern in which there were two intervals of monoexponential emptying, interrupted by an interval with no emptying.

An example of each type of emptying pattern is shown in Fig. 1.

Table III. *Values for emptying pattern characterized by two monoexponential phases separated by a lag phase; Type 3 emptying pattern*

Subject	*Treatment*	$K_G(min^{-1})$ *for first phase*	*Duration of lag (min)*	$K_G(min^{-1})$ *for second phase*
2	Control	0.0425	20	0.0315
4	Meperidine	0.0047	50	0.0084
5	Meperidine*	0.0112	0	0.0385
7	Meperidine	0.0036	0	0.0094
7	Pentazocine†	0.0047	0	0.0105

*In this experiment there was an initial "squirt" of 30% of the stomach contents into the small intestine.
†In this experiment there was an initial lag period of 25 min during which no emptying was observed.

In the control studies, 50% of ingested solution was emptied in a mean time of 12 min (range, 4 to 22 min) (Tables I to III). Gastric emptying was usually of the Type 2 pattern with very fast initial emptying of a mean of 30% (range, 9 to 65%) followed by a slower monoexponential emptying with a mean t½ of 25 min (Table II).

With the narcotic analgesics emptying was either Type 1 or Type 3. The mean time for 50% gastric emptying was increased to 90 min (range, 30 to 127) and after pentazocine followed by naloxone the time for 50% gastric emptying was 30 min (range, 4 to 46).

With Types 1 and 3 emptying a lag period was observed, ranging from 0 to 36 min (Tables I and III). In most cases the longer lag periods were associated with pretreatment with a narcotic.

Acetaminophen absorption. The mean plasma concentrations of unconjugated acetaminophen are shown in Table IV.

In all the control studies acetaminophen absorption was rapid with a mean peak plasma concentration of 21.8 $\mu g\ ml^{-1}$ occurring at 23 min. Following administration of the narcotic analgesics, absorption was delayed. The individual mean peak plasma concentrations were 17.9 $\mu g\ ml^{-1}$ and 8.3 $\mu g\ ml^{-1}$ at 111 and 120 min after meperidine and pentazocine, respectively.

Pharmacokinetic analyses.

Schema 1. The plasma acetaminophen concentration–time plots appeared to follow a smooth curve in most cases, and computer analyses provided an estimate of the apparent absorption rate constant (K_A) (Table V) based on the model of Schema 1. In some studies where meperidine and pentazocine were administered, there was a "lag" period during which the plasma concentration rose only slowly before the rapid rise at the end of the "lag" phase. These early points could not be included in the calculated curve, and so the apparent absorption rate constant was based on the rapidly ascending part of the curve. In Subject 2 two peaks were observed in the control study and no attempt was made to draw a calculated curve to fit these data.

Overall, there was no significant correlation between K_A and K_G ($r = 0.31$; $p' > 0.1$; $n = 13$), but, for the Type 1 emptying pattern the individual observed values for K_A and K_G were similar. There was a highly significant correlation ($r = 0.97$; $p' < 0.01$; $n = 6$) and the slope of the regression line did not differ significantly from unity ($p' = 0.10$) (Fig. 2).

Thus, the values of K_A and K_G were not equal in most cases because gastric emptying pattern was not a simple monoexponential process. The model shown in Schema 1 therefore has limited application for the description of the kinetics of absorption of drugs such as acetaminophen.

Schema 2. Analysis of the data using the model of Schema 2 revealed excellent agreement between observed and calculated plasma concentration–time curves in all subjects, regardless of the type of gastric emptying pattern. The analysis provided an estimate of K_A^*, the rate constant for transfer of drug from the small intestine into the systemic circulation. The values of K_A^* were greater than K_G, indicating that the rate-limiting step in the overall absorption of

Table IV. *Mean plasma concentrations ($\mu g\ ml^{-1}$) of unconjugated acetaminophen after oral dose of aqueous solution (20 mg kg^{-1})*

	Time after administration (min)								
	3	*5*	*6*	*10*	*15*	*20*	*25*	*30*	*40*
Control study, 8 subjects									
Mean	1.8	—	7.5	15.0	17.5	19.6	20.0	18.8	17.2
Standard deviation	2.6	—	4.4	7.3	7.9	7.2	5.2	4.0	3.1
150 mg IM meperidine 30 min before ingestion, 4 subjects									
Mean	—	1.7	—	2.7	3.4	3.8	4.3	5.3	6.8
Standard deviation	—	2.9	—	5.2	5.7	6.3	7.2	9.1	11.5
60 mg IM pentazocine 30 min before ingestion, 4 subjects									
Mean	—	0.6	—	1.3	1.6	2.2	2.9	3.8	4.0
Standard deviation	—	1.1	—	2.6	2.7	3.0	3.4	4.0	3.8
60 mg IM pentazocine 30 min before and 1.2 mg IV naloxone immediately before ingestion, 4 subjects									
Mean	—	1.3	—	3.3	8.7	14.5	14.6	14.4	11.6
Standard deviation	—	0.1	—	1.1	4.8	3.0	4.2	4.5	2.4

Table V. *Kinetic values for acetaminophen after oral administration to human volunteers (20 mg kg^{-1} body weight)*

Subject	*Treatment*	*Peak plasma concentration $\mu g\ ml^{-1}$*	*Time of peak (min)*	*Apparent absorption rate constant* (K_A), min^{-1}*	*True absorption rate constant† (K_A*), min^{-1}*
1	Control	27.9	15	0.054	0.255
1	Pentazocine/naloxone	14.5	15	0.076	0.071
2	Control	25.2, 23.0	20,60	‡	0.134
2	Meperidine	23.0	75	0.020	0.077
2	Pentazocine	11.9	60	0.005	0.214
2	Pentazocine/naloxone	21.1	30	0.019	0.209
3	Control	24.4	10	0.066	0.061
3	Pentazocine	9.2	180	0.013	0.066
3	Pentazocine/naloxone	14.1	20	0.031	0.077
4	Control	19.4	40	0.017	0.082
4	Meperidine	16.8	210	0.008	0.047
5	Control	31.1	20	0.049	0.171
5	Meperidine	24.1	40	0.015	0.118
6	Control	17.5	25	0.035	0.153
7	Control	17.7	20	0.046	0.218
7	Meperidine	7.7	120	0.014	0.256
7	Pentazocine	11.2	180	0.009	0.210
7	Pentazocine/naloxone	12.7	25	0.027	0.173
8	Control	15.7	25	0.038	0.050
	Mean				0.139
	Standard deviation				0.073

*Based on model of Schema 1.
†Based on model of Schema 2.
‡Conventional analysis of these data was inappropriate.

50	*60*	*75*	*90*	*120*	*150*	*180*	*210*	*240*	*360*	*480*
15.0	15.1	14.2	12.0	10.3	—	7.4	—	5.1	2.7	1.4
2.7	4.0	3.3	2.9	3.1	—	2.2	—	1.7	1.5	0.7
8.2	10.0	12.3	13.8	14.3	12.1	11.5	11.4	9.8	5.1	2.6
8.5	7.3	8.8	7.8	4.9	3.4	4.2	5.1	3.4	2.0	1.3
4.6	5.5	7.0	8.8	10.0	10.3	10.7	—	7.4	4.4	2.8
4.2	5.0	3.4	2.1	1.7	0.7	1.3	—	1.6	1.4	1.3
11.0	11.2	10.9	10.7	9.4	—	6.9	—	5.3	2.7	1.6
3.1	3.3	2.7	2.9	2.3	—	1.9	—	1.4	0.8	0.7

acetaminophen is the rate of gastric emptying (Tables I to III, Table V).

Fig. 3 shows the observed and calculated plasma concentrations and the observed gastric emptying pattern (Type 1) in Subject 2. Meperidine delayed the onset of emptying in this subject by about 35 min, and the quiescent period was reflected in a delay before the plasma concentrations rose. The data suggest that a small amount of solution had emptied from the stomach in the quiescent period, and this is seen as a small rise in plasma concentrations.

Fig. 4 shows the plasma concentration–time profile and gastric emptying pattern for Type 2 gastric emptying in subject 6. About one-third of the dose left the stomach rapidly and the plasma concentration rose correspondingly. In the subsequent exponential phase, gastric emptying was rapid (K_G equal to 0.050 min^{-1}). Since K_A* was even larger (0.153 min^{-1}), the quantity of acetaminophen in the small intestine fell rapidly.

The measured plasma concentrations of acetaminophen in one subject showed two peaks. The gastric emptying pattern indicated that there were two exponential portions separated by an interval of about 20 min during which there was no emptying. Using an analog computer program with the times of start (t_1) and end (t_2) of the quiescent interval, and the rate constants $K_{G(1)}$ and $K_{G(2)}$ for the first and second exponential emptying periods, respectively, the calculated plasma concentration–time curve agreed remarkably well with the observed points (Fig. 5).

In a process with two consecutive steps, estimation of the rate constant for the faster step is subject to some error. Successive increases in K_A*,with K_G held constant and of similar magnitude to K_A*, make substantial changes in the predicted curve (Fig. 6). However, if $K_A^* >> K_G$, the rate constant for the overall process of transfer from stomach to systemic circulation is approximately equal to K_G, and the predicted plasma concentration–time curve is influenced only slightly by small changes in K_A*.

Discussion

Gastric emptying patterns in the 19 studies showed considerable variation but could be conveniently classified into three types. Departures of emptying from the simple monoexponential pattern are well recognized in the litera-

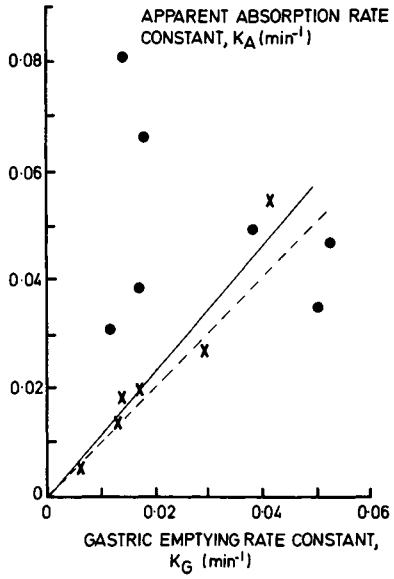


Fig. 2. Apparent absorption rate constant (K_A) plotted against gastric emptying rate constant (K_G) in studies showing Type 1 (X) and Type 2 (•) gastric emptying patterns. ----, Line of identity; ——, regression line for Type 1 emptying.

ture.[6] Inspection of the emptying pattern and plasma acetaminophen concentration–time curve for each experiment showed that the two were closely related. In particular, where the start of gastric emptying was delayed there was a corresponding "lag" period during which the plasma concentration did not rise or rose only very slightly and slow gastric emptying was associated with a slow rise in plasma concentration. Conversely, the most rapid increases in acetaminophen concentrations were found with Type 2 gastric emptying, particularly when a substantial proportion of the dose emptied in the initial "squirt." This obvious relationship between gastric emptying and the initial rise in plasma concentration strongly suggest that gastric emptying was the rate-limiting step in the absorption of acetaminophen.

Overall, the values obtained for K_A using conventional pharmacokinetic analysis did not correspond to the observed values of K_G, but these two values were in excellent agreement when there was Type 1 gastric emptying. This is to be expected since emptying is then a single exponential process which limits absorption. There was no significant correlation between K_G and K_A with Types 2 and 3 gastric emptying patterns and Schema 2 was developed to take these patterns into account. Using this model there was good agreement between calculated and actual plasma concentrations in all cases. Even when gastric emptying was interrupted by a quiescent period and the plasma concentration–time curve had two peaks, satisfactory agreement was found using the model (Fig. 5). The occurrence of two peaks early in the plasma concentration–time curve observed here and in other studies is seen to be due to an interruption in gastric emptying. The first rapid decline in plasma concentration starts at the time when emptying from the stomach temporarily ceases.

As expected, the true absorption rate constant K_A* (Schema 2) exceeded the apparent absorption rate constant K_A (Table V). Since there was no significant correlation between K_A* and K_A, the true absorption rate constant cannot be predicted from K_A obtained by conventional pharmacokinetic analysis. The absolute bioavailability was not determined in this investigation. Since Rawlins, Henderson, and Hijab[14] found that the mean bioavailability of acetaminophen from two 500-mg tablets was 89%, the apparent absorption rate constants (Table V) should be corrected for incomplete bioavailability, but this does not alter the conclusions drawn. The concurrent administration of narcotic analgesics does not influence the total urinary excretion of acetaminophen and its major metabolites.[9]

The value of K_A* was greater than K_G in all experiments and confirms that gastric emptying is the rate-limiting step in the absorption of acetaminophen given orally in solution. Absorption from the small intestine is rapid, and the estimated mean t½ for absorption is 6.8 ± 0.9 min (SE). The results of our study confirm that absorption of acetaminophen was highly dependent on the kinetics of gastric emptying.

Body position has recently been shown to alter the absorption of acetaminophen from tablets taken by mouth,[10] presumably by influencing gastric emptying. Our work demonstrates that even under carefully controlled conditions there is considerable individual variation in gastric emptying and acetaminophen absorption from a solution.

Most control studies showed Type 2 gastric

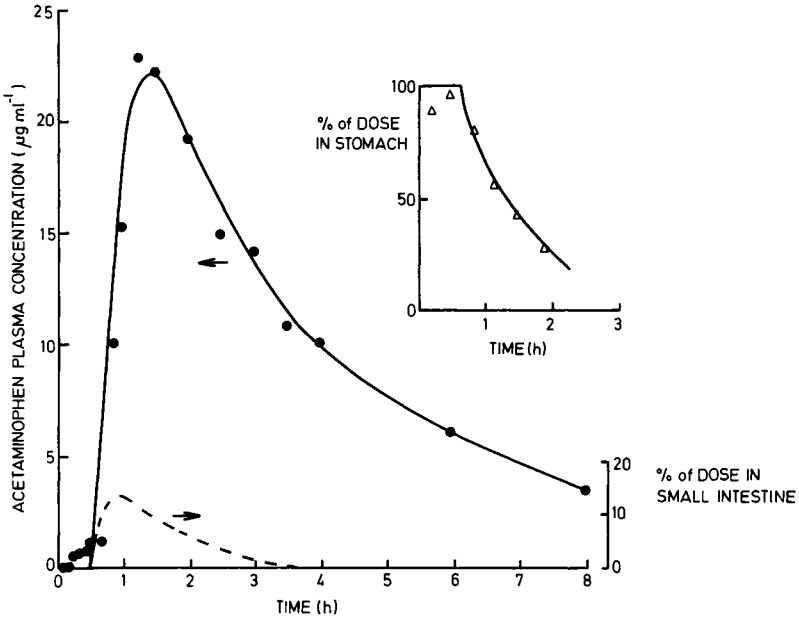


Fig. 3. Plasma acetaminophen concentration plotted against time for Type 1 emptying with a lag period (Subject 2, meperidine). • Data points; ——, calculated curve; ----, predicted percentage of dose in small intestine. *Inset,* Gastric emptying pattern. △, Data points; ——, calculated curve.

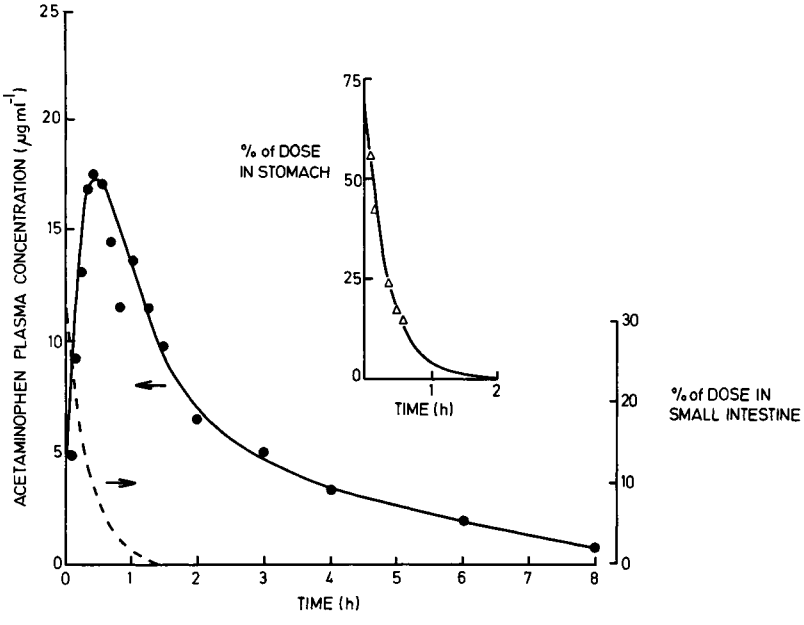


Fig. 4. Plasma acetaminophen concentration plotted against time for Type 2 gastric emptying (Subject 6, control). •, Data points; ——, calculated curve; ----, predicted percentage of dose in small intestine. *Inset,* Gastric emptying pattern. △, Data points; ——, calculated curve.

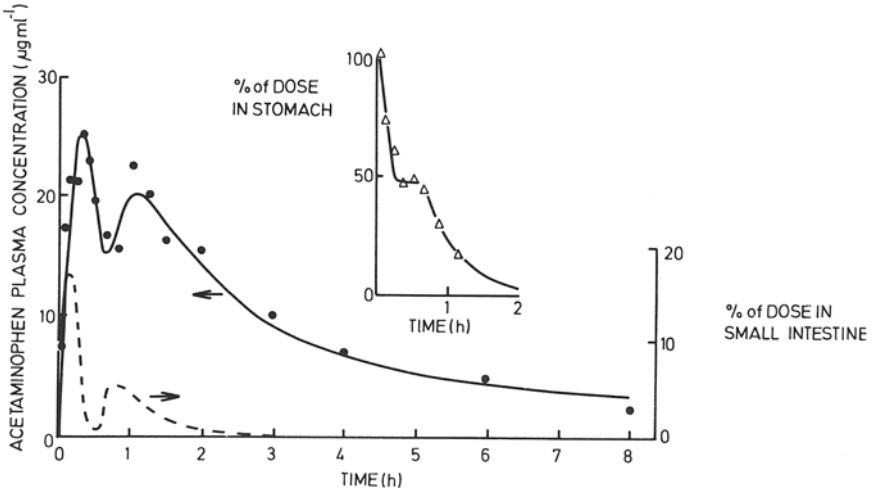


Fig. 5. Plasma acetaminophen concentration plotted against time for Type 3 gastric emptying (Subject 2, control). •, Data points; ——, calculated curve; ----, predicted percentage of dose in small intestine. *Inset,* Gastric emptying pattern. △, Data points; ——, calculated curve.

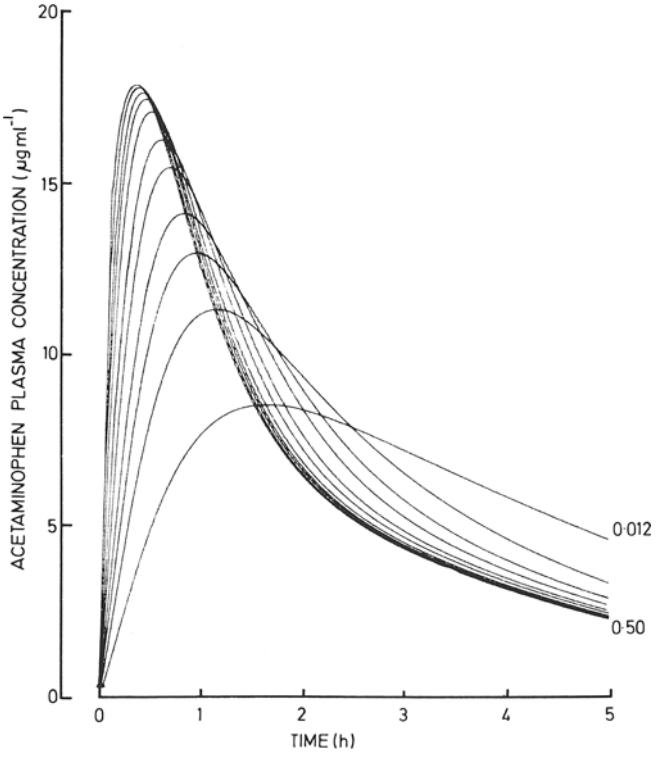


Fig. 6. Predicted plasma concentration–time curves showing the effects of change in K_A*. (Subject 6, control study. Type 2 gastric emptying: f_1 = 34%, f_2 = 66%; K_G = 0.050; K_{12} = 0.016; K_{21} = 0.011; K_{el} = 0.010 min^{-1}). Values of K_A* for successive curves are: 0.012, 0.025, 0.038, 0.05, 0.075, 0.10, 0.15, 0.20, 0.25, 0.35, and 0.50 min^{-1}.

emptying but the percentage of the dose emptied as an initial bolus varied from 9% to 65%. When a large proportion of the dose rapidly entered the small intestine, plasma acetaminophen concentration rose rapidly and the apparent absorption rate constant (K_A) approached that for the true absorption rate constant (K_A*). However, when only a small amount was released from the stomach in the first bolus, K_A* was 3 to 5 times as great as K_A.

Premedication with a narcotic analgesic abolished the initial bolus in seven out of eight studies and emptying was arrested or greatly reduced. Plasma concentrations remained at or close to zero for about 30 to 40 min. In some cases a very slow rise was observed to concentrations of about 5% to 10% of the peak values (Fig. 3); this may be due to a small amount of solution passing through the pylorus (since the emptying measurements did show a small loss of solution from the stomach), or to a small amount of acetaminophen that may have been absorbed from the stomach.

In one study (Subject 5, post-meperidine) an initial bolus of 30% of the dose entered the small intestine. The plasma concentration rose immediately after ingestion of the solution. Subsequent gastric emptying was much slower than in the control and the peak plasma concentration was lower. The reason for the reduced or delayed effect of meperidine on this subject is not known.

Measurements of gastric emptying have confirmed that it is not usually a simple monoexponential process in supine individuals. Type 2 gastric emptying is more common, and when a large proportion of the dose passes through the pylorus, absorption is very rapid. Using a model in which separate compartments represent the stomach and the small intestine, it is possible to calculate plasma concentrations arising from several patterns of gastric emptying and to estimate the true absorption rate constant (K_A*) for absorption from the small intestine. Although simpler models such as that of Schema 1 may be consistent with experimental data, the proposed model seems to be more appropriate for the description of drug absorption from orally administered solutions if gastric emptying is to be taken into account.

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